FULL PAPERS

Readily Synthesized Chiral Sulfides as Reagents for Asymmetric Epoxidation

D. Michael Badine, Christina Hebach, and Varinder K. Aggarwal*[a]

Abstract: Chiral oxathianes were designed, synthesized, and successfully used for asymmetric sulfur ylide mediated epoxidation. A considerable emphasis has been placed upon the design of sulfides with suitable architecture in a small number of steps (three or four). The use of (4aR,6S,8aR)-6-isopropenyl-8a-methyloctahydro-1,4-benzoxathiane in asymmetric epoxidation resulted in good diastereo- and enantioselectivity in t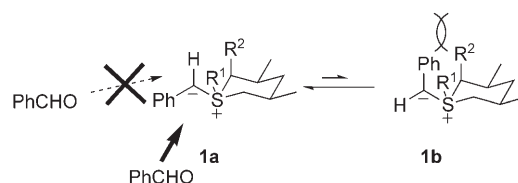he formation of stilbene oxide, and (2S,6S)-2-allyl-2,3,3,6-tetramethyl-1,4-oxathiane produced even better results. Moderate to good diastereoselectivities with essentially complete enantioselectivities were observed in the formation of alkyl–aryl-, vinyl–aryl-, and propargyl–aryl-substituted epoxides. The selectivities were rationalized and supported by density functional theory calculations.

Keywords: asymmetric synthesis · chiral sulfides · epoxidation · sulfur ylides · synthesis design
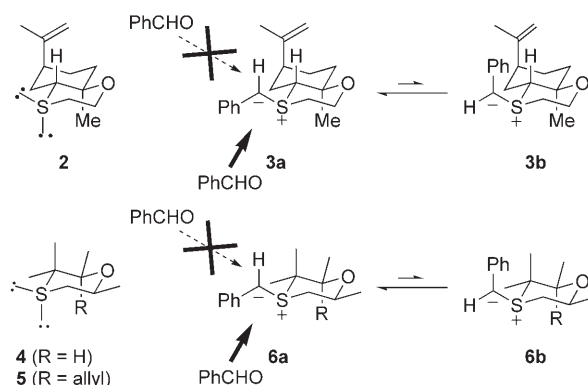
Introduction

The reactions of sulfur ylides with carbonyl compounds have emerged as a useful and powerful method in the arsenal of asymmetric transformations.[1–3] Two processes have been developed: a catalytic one which shows somewhat limited substrate scope[4–6] and a more general stoichiometric process.[7,8] A process that uses stoichiometric amounts of chiral sulfides clearly requires ready access, and on a large scale, to such material, so we began a program of research to deliver this. In addition to ready availability in a short number of steps, certain structural features are required to promote high selectivity.[9–11] We have identified the most important factors that control enantioselectivity as ylide conformation and ylide face selectivity.[9] If the sulfide is incorporated into a six-membered ring, both of these factors can be controlled by judicious choice of the substituents R^1 and R^2 (Scheme 1). Other requirements include sufficient reactivity and high diastereoselectivity in the sulfide-alkylation step and control in the conformation of the thiane.

Based on the above criteria, conformationally locked chiral sulfides **2**, **4**, and **5** were designed (Scheme 2). In each case alkylation was expected to occur at the more accessible equatorial lone pair of electrons, and ylide conformation

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Scheme 1. Facial selectivity and conformational control.

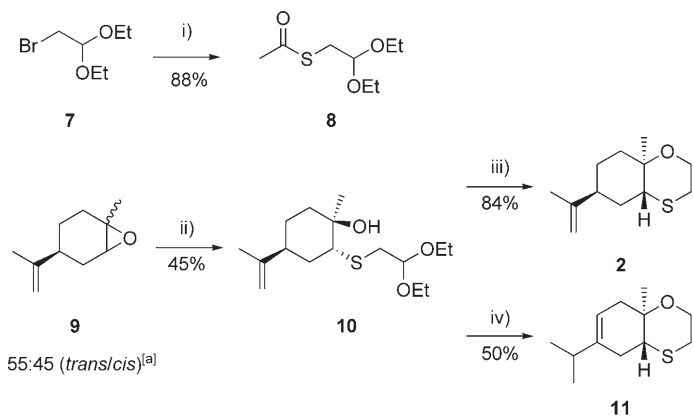Scheme 2. Design features of sulfides **2**, **4**, and **5**.

and face selectivity would be controlled by the substituents at the 2-position of the oxathiane ring. The oxygen atom of the oxathiane was incorporated to facilitate synthesis.

Results and Discussion

Sulfide **2** was synthesized in three steps (Scheme 3). The thioacetate acetal precursor **8** was obtained in 88% yield by

Scheme 3. Synthesis of sulfides **2** and **11**: Reagents and conditions: i) KSAc, DMF, RT, 24 h; ii) **8**, NaOMe, MeOH, RT, 18 h; iii) BF$_3$·OEt$_2$ (1 equiv), Et$_3$SiH (5 equiv), CH$_2$Cl$_2$, 18 h; iv) TMSOTf (5 equiv), Et$_3$SiH (5 equiv), CH$_2$Cl$_2$, RT, 18 h. DMF = *N*,*N*-dimethylformamide, Tf = tri-fluoromethanesulfonyl, TMS = trimethylsilyl. [a] The *trans* diastereomer of **9** has the methyl and propenyl groups on opposite sides of the cyclo-hexane ring.

reaction of bromoacetal **7** with potassium thioacetate.[12] The thioacetate **8** underwent reaction with the commercially available mixture of (−)-*cis*- and *trans*-limonene oxide **9** in the presence of sodium methoxide in methanol to give the hydroxy sulfide **10** as a single diastereomer in 45% yield. In this process, the reactive thiolate anion is generated in situ. This procedure is especially useful as it avoids the handling of the intermediate thiol, which we found to be prone to ox-idative disulfide formation. Furthermore, a highly selective kinetic resolution occurs in this process: only the *trans* isomer reacts, leaving the *cis* isomer in solution. This type of kinetic resolution has been observed previously[13] and is a consequence of the *trans* isomer undergoing ring opening via an energetically favorable "chair-like" transition state, whereas the *cis* isomer must pass through a less-favorable "boat-like" transition state. The acetal **10** was then subjected

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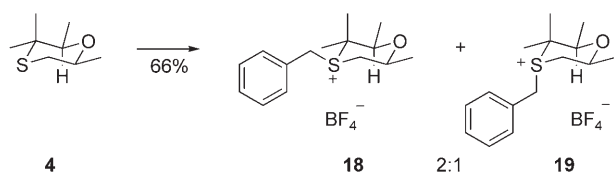
to a reductive ring-closure reaction mediated by boron tri-fluoride etherate to provide the target sulfide **2** in good yield. In contrast, an excess of trimethylsilyl trifluorometh-anesulfonate (5 equiv) as Lewis acid resulted in alkene iso-merization and ring closure to give the product **11**.

Chiral sulfides **2** and **11** were alkylated to give single dia-stereomers of sulfonium salts **12** and **13**, respectively, by using benzyl bromide and sodium tetrafluoroborate under biphasic conditions (Scheme 4). In these reactions, the rela-tively nucleophilic bromide ion is exchanged for the less-nu-cleophilic tetrafluoroborate counterion to avoid reversion to the starting materials.
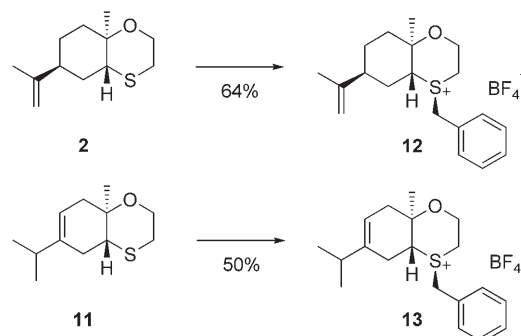
Scheme 4. Alkylation of sulfides **2** and **11**: Reagents and conditions: BnBr, NaBF$_4$, CH$_2$Cl$_2$/H$_2$O (1:1), room temperature, 48 h.

The synthesis of chiral sulfide **4** followed similar lines to sulfide **2** and was efficiently prepared in four steps (Scheme 5). The first step involved the synthesis of the known bromide **15**,[14] and the second step its conversion
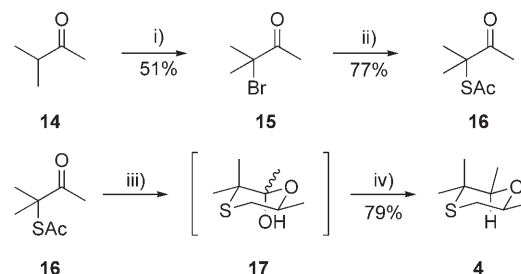
Scheme 5. Synthesis of sulfide **6**. Reagents and conditions: i) Br$_2$, CCl$_4$, reflux, 4 h; ii) KSAc, DMF, room temperature, 18 h; iii) NaSMe, MeOH, propylene oxide, room temperature, 4 h; iv) BF$_3$·OEt$_2$, Et$_3$SiH, CH$_2$Cl$_2$, room temperature, 18 h.

into the requisite thioacetate precursor **16**. This then reacted with sodium thiomethoxide in the presence of propylene oxide, and the crude mixture of lactols **17** was reduced with boron trifluoride etherate in the presence of triethylsilane to give the sulfide **4** in 79% yield.

Sulfide **4** required more-forcing alkylation conditions than sulfides **2** or **11**, indicating that it was substantially more hin-dered. Silver tetrafluoroborate was used to mediate the re-action of **4** with benzyl bromide (Scheme 6).[7] However, when this sulfide was alkylated, a mixture of sulfonium salt diastereomers **18** and **19** resulted. This meant that one of

the criteria outlined in the Introduction was not being fulfilled as both lone electron pairs of sulfide **4** were reactive.

A way to block reaction of the axial lone electron pair of **4** would be to incorporate an axial substituent on the carbon

Scheme 6. Alkylation of sulfide **4**. Reagents and conditions: BnBr, AgBF₄, acetone, 40 °C, 18 h.

adjacent to the oxygen atom. It was anticipated that this could be achieved by treating **17** with boron trifluoride etherate in the presence of a nucleophile other than hydride. Thus, thioacetate **16** was treated with (*S*)-propylene oxide, and the resulting mixture of lactols **17** was treated with boron trifluoride etherate and triethylallyl silane. This resulted in the formation of the desired chiral sulfide **5** in 78 % yield (Scheme 7).
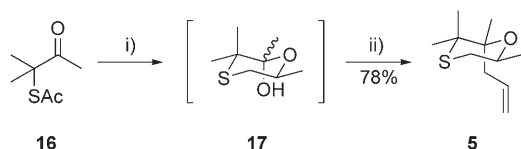
Scheme 7. Synthesis of sulfide **5**. Reagents and conditions: i) KOH, MeOH/H₂O, (*S*)-propylene oxide, room temperature, 4 h; ii) BF₃·OEt₂, Et₃SiCH₂CH=CH₂, CH₂Cl₂, room temperature, 18 h.

Sulfide **5** proved to be incompatible with the silver tetrafluoroborate-mediated alkylation conditions employed for sulfide **4**, and a complicated reaction mixture resulted. This is most likely due to the presence of the alkene, which presumably coordinates and reacts with silver tetrafluoroborate. However, sulfide **5** was successfully alkylated by using an acid-mediated alkylation with benzyl alcohol[15] to give a single diastereomer of sulfonium salt **20**, the result of alkylation of the equatorial lone pair of electrons on the sulfur atom (Scheme 8). Thus, the extra bulk of the allyl moiety proved sufficient to block alkylation of the axial lone electron pair of **5**.

The chiral sulfonium salts **12**, **13**, and **20** were treated with base and benzaldehyde under two sets of reaction conditions to evaluate their potential for asymmetric epoxidation
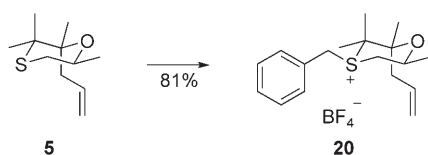
Scheme 8. Alkylation of sulfide **5**. Reagents and conditions: BnOH, HBF₄, dioxane, room temperature, 4 h.

(Table 1): Method A: KOH, EtOH, −50 °C, and Method B: EtP₂ base (*N,N,N′,N′*-tetramethyl-*N′′*-[tris(dimethylamino)-phosphoranylidene]phosphoric triamide ethylamine),

Table 1. Results for stoichiometric asymmetric epoxidation with sulfonium salts **12**, **13**, **20**, and **21**.
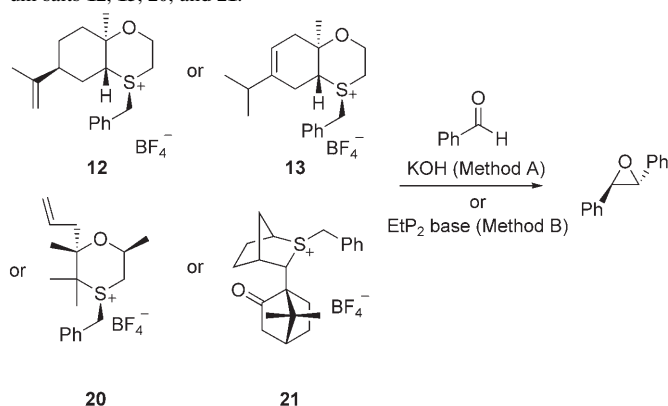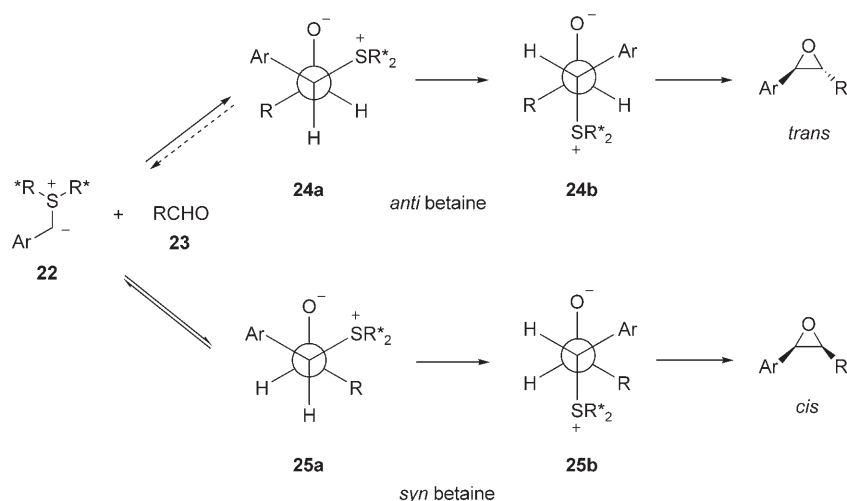
Entry	Salt	Aldehyde	Method[a]	Yield [%][b]	d.r. (*trans/cis*)	*ee* [%]
1	**12**	benzaldehyde	A	54	72:28	89[c]
2	**13**	benzaldehyde	A	58	54:46	91[c]
3	**20**	benzaldehyde	A	56	79:21	93[c]
4	**12**	benzaldehyde	B	75	99:1	87[c]
5	**13**	benzaldehyde	B	67	72:28	80[c]
6	**20**	benzaldehyde	B	78	99:1	> 99[c]
7	**20**	methacrolein	B	67	99:1	> 99[c]
8	**20**	cinnamaldehyde	B	91	93:7	99[c]
9	**20**	TIPS-propargyl-aldehyde	B	70	70:30	99[c] 87[d]
10	**20**	valeraldehyde	B	99	70:30	> 99[c] > 99[d]
11	**21**[7]	valeraldehyde	B	64	92:8	97[c]

[a] Method A: aldehyde, KOH, EtOH, −50 °C. Method B: aldehyde, EtP₂ base, CH₂Cl₂, −78 °C; [b] yield of isolated product; [c] *ee* (*trans*); [d] *ee* (*cis*). TIPS = triisopropylsilyl.

CH₂Cl₂, −78 °C. Also included for comparison is the result of epoxidation with sulfonium salt **21**.[7] The results show that use of protic solvents (Method A) leads to lower diastereoselectivity than with aprotic solvents (Method B) (compare entries 1–3 with entries 4–6). This can be rationalized based on our understanding of the factors that control diastereoselectivity.[9] The high *trans* selectivity observed under aprotic conditions is a result of unproductive, reversible formation of the *syn* betaine **25a** (Scheme 9). This compound, though easily formed, suffers a high activation barrier to bond rotation as two large groups have to pass each other, so it reverts to the starting materials instead. Under protic conditions, the barriers to bond rotation in the betaines are reduced because the charges are better solvated and so more easily separated. Thus, *syn* betaine formation becomes partially productive, leading to mixtures of *trans* and *cis* epoxides.

The diastereo- and enantioselectivities obtained for epoxidations with sulfonium salt **20** were significantly superior to

Scheme 9. Reversible *syn* betaine formation leading to high *trans* selectivity in epoxidation.

with geometry optimization at the B3LYP/6-31* level followed by single-point calculations at the B3LYP/6-311G**+ level in acetonitrile.[17] Indeed, the energy difference between **3a** and **3b** (1.69 kcal) was significantly smaller than that calculated for ylides **26a** and **26b** (4.37 kcal)[10] and ylides **6a** and **6b** (3.78 kcal) and is, therefore, most likely to be responsible for the lower enantioselectivities with sulfonium salt **12** (and by analogy **13**) compared to sulfonium salts **20** and **21** (Scheme 10).

those with **12** and **13** (compare entries 4–6), so other aldehydes were explored with this salt (entries 7–10), and again good yields were accompanied by excellent enantioselectivities. The yield and selectivity obtained with **20** compare favorably with those obtained with sulfonium salt **21** (compare entry 10 with 11). Sulfonium salt **21** was previously found to be highly effective in stoichiometric epoxidation, but a five-step synthesis is required to obtain the parent sulfide.[4]

The good to excellent enantioselectivity observed with salts **12**, **13**, and **20** results from the design features discussed in Scheme 2. We believe that the facial selectivity of all the ylides is well-controlled and that the relatively low enantioselectivity with the sulfonium salts **12** and **13** compared to **20** (and **21**) is likely to be poor conformational control of the ylide (Scheme 2). To investigate this issue further, we calculated the relative energies of the ylide conformers. For this we used density functional theory (DFT) calculations

Conclusions

Readily synthesized chiral sulfides have been designed and employed in asymmetric epoxidation. Chiral sulfide **2** is most easily synthesized, but superior selectivities were observed with chiral sulfide **5**. This sulfide has been shown to be an extremely effective reagent, providing aryl–alkyl-, aryl–aryl-, aryl–vinyl-, and aryl–alkynyl-substituted epoxides in high yields and enantioselectivities. These sulfides provide further validation of the model that accounts for both diastereo- and enantioselectivity, thus providing further evidence of its use as a predictive tool in the design of new chiral sulfides.

Experimental Section

For general procedures, see the Supporting Information.

8:[12] Potassium thioacetate (12.50 g, 110 mmol) was weighed under nitrogen and added in one portion to a solution of **7** (11 mL, 73 mmol) in *N,N*-dimethylformamide (DMF; 190 mL, anhydrous). The colorless solution became turbid and green before turning brown. After being stirred for 18 h at room temperature, the reaction mixture was diluted with diethyl ether (200 mL) and washed with water (4×200 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to chromatography (EtOAc (5%) in petrol) to produce **8** as a colorless, pungent oil (12.31 g, 88%). $R_f = 0.37$ (EtOAc (10%) in petrol); IR (neat): $\tilde{\nu} = 1692$ (C=OS), 1040 cm^{-1} (C–O); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): $\delta = 4.50$ (t, $^3J_{H,H} = 5.5$ Hz, 1H; C*H*(OEt)$_2$), 3.65 (dq, $^2J_{H,H} = 9.5$ Hz, $^3J_{H,H} = 7.0$ Hz, 2H; 2CH$_3$C*H*H), 3.55 (dq, $^2J_{H,H} = 9.5$ Hz, $^3J_{H,H} = 7.0$ Hz, 2H; 2CH$_3$CH*H*), 3.12 (d, $^3J_{H,H} = 5.5$ Hz, 2H; CH$_2$S), 2.35 (s, 3H; CH$_3$CO), 1.23 ppm (t, $^3J_{H,H} = 7.0$ Hz, 6H; 2CH$_3$);[16] ^{13}C NMR (101 MHz, CDCl$_3$, 25°C): $\delta = 195.2$ (s), 101.3 (d), 62.4 (t), 32.4 (t), 30.4 (q), 15.2 ppm (q).[16]

10: Sodium methoxide (3.37 g, 62.0 mmol) was added with stirring to a solution of **9** (*trans/cis* = 55:45, 20.5 mL, 125 mmol) and **8** (12.0 g, 62.0 mmol) in methanol (500 mL) at 0°C. The solution was warmed to room temperature and after 18 h was concentrated under vacuum. The residue was dissolved in CH$_2$Cl$_2$ (100 mL) and HCl (1 N, 50 mL). The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (3×50 mL). The organic layers were combined, washed with brine (2×50 mL), dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue
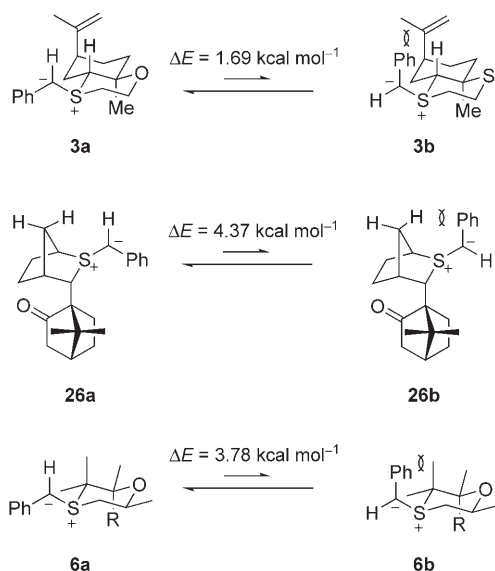
Scheme 10. Results of DFT calculations on ylides **3**, **26**, and **6**.

was subjected to chromatography (EtOAc (20%) in petrol) to yield **10** as a colorless, sweet-smelling oil (16.6 g, 45%). $R_f = 0.19$ (EtOAc (10%) in petrol); $[\alpha]_D^{24} = -70.5$ ($c = 1.0$ in CHCl$_3$); IR (neat): $\tilde{\nu} = 3456$ (O−H), 1643 (C=C), 1371 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): $\delta = 4.78$ (br s, 1H; CHH=), 4.76 (br s, 1H; CHH=), 4.61 (t, $^3J_{H,H} = 5.5$ Hz, 1H; CH(OEt)$_2$), 3.69 (dq, $^2J_{H,H} = 9.5$ Hz, $^3J_{H,H} = 7.0$ Hz, 1H; CH$_3$CHHO), 3.67 (dq, $^2J_{H,H} = 9.5$ Hz, $^3J_{H,H} = 7.0$ Hz, 1H; CH$_3$CHHO), 3.56 (dq, $^2J_{H,H} = 9.5$ Hz, $^3J_{H,H} = 7.0$ Hz, 1H; CH$_3$CHHO), 3.54 (dq, $^2J_{H,H} = 9.5$ Hz, $^3J_{H,H} = 7.0$ Hz, 1H; CH$_3$CHHO), 2.94 (t, $^3J_{H,H} = 4.0$ Hz, 1H; CH_{eq}S), 2.77 (d, $^3J_{H,H} = 5.5$ Hz, 2H; CH$_2$S), 2.35–2.25 (m, 1H; CHC=), 2.14 (ddd, $^2J_{H,H} = 13.5$ Hz, $^3J_{H,H} = 9.5, 4.0$ Hz, 1H; CH_{ax}HCHS), 1.90 (br s, 1H; OH), 1.8–1.5 (m, 8H; 2×CH$_2$, CHH, CH$_3$C=C), 1.36 (s, 3H; CH$_3$CO), 1.24 (t, $^3J_{H,H} = 7.0$ Hz, 3H; CH_3CH$_2$), 1.22 ppm (t, $^3J_{H,H} = 7.0$ Hz, 3H; CH_3CH$_2$); ^{13}C NMR (101 MHz, CDCl$_3$, 25°C): $\delta = 148.7$ (s), 109.3 (t), 103.1 (d), 72.5 (s), 62.1 (t), 62.0 (t), 53.8 (d), 38.6 (d), 36.5 (t), 34.8 (t), 33.1 (t), 27.8 (q), 26.2 (t), 21.3 (q), 15.3 ppm (2×q); MS (CI): m/z (%): 285 (19) [MH−H$_2$O], 256 (34) [M−EtOH], 239 (74), 103 (100); elemental analysis: calcd (%) for C$_{16}$H$_{30}$O$_3$S (302.5): C 63.5, H 10.00; found: C 63.4; H 10.30.

2:[15] Boron trifluoride diethyletherate (distilled, 2.51 mL, 19.8 mmol) was added to a solution of **10** (6.00 g, 19.8 mmol) and triethylsilane (15.8 mL, 99.2 mmol) in CH$_2$Cl$_2$ (300 mL) at 0°C. The mixture was warmed to room temperature for 18 h. It was then poured into saturated aqueous sodium carbonate (100 mL), and the resulting mixture was separated and washed with more sodium carbonate (2×100 mL) and brine. The solution was then dried over magnesium sulfate, filtered, and concentrated under vacuum. Chromatography (EtOAc (5%) in petrol) provided **2** as white needles (3.4 g, 81%). $R_f = 0.60$ (EtOAc (30%) in petrol); m.p.: 33–36°C (EtOAc/petrol); $[\alpha]_D^{20} = -280.0$ ($c = 0.1$ in CHCl$_3$); IR (neat): $\tilde{\nu} = 3087$ (C=CH$_2$), 1075 (C−O), 1045 cm^{-1} (C−O); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): $\delta = 4.98$ (br q, $^4J_{H,H} = 1.5$ Hz, 1H; HC=), 4.91 (br s, 1H; HC=), 4.00 (ddd, $^2J_{H,H} = 12.5$ Hz, $^3J_{H,H} = 10.0, 2.0$ Hz, 1H; CHHO$_{ax}$), 3.80 (ddd, $^2J_{H,H} = 12.5$ Hz, $^3J_{H,H} = 3.5, 2.0$ Hz, 1H; CHHO$_{eq}$), 3.05 (ddd, $^2J_{H,H} = 12.5$ Hz, $^3J_{H,H} = 10.0, 3.5$ Hz, 1H; CHHS$_{ax}$), 3.00 (dd, $^3J_{H,H} = 12.5, 2.5$ Hz, 1H; CHS), 2.38–2.31 (br m, 1H; CHC=C), 2.35 (dt, $^2J_{H,H} = 12.5$ Hz, $^3J_{H,H} = 2.0$ Hz, 1H; CHHS$_{eq}$), 2.03–1.96 (m, 1H; CHHCHC=C), 1.86–1.70 (m, 2H; CHHCHS, CHHCHC=C), 1.75 (br s, 1H; CH$_3$C=C), 1.63 (td, $^2J_{H,H} = 13.0$ Hz, $^3J_{H,H} = 13.0, 4.0$ Hz, 1H; HCHCO$_{ax}$), 1.54 (ddd $^2J_{H,H} = 13.0$, $^3J_{H,H} = 4.5, 3.0$ Hz, 1H; HCHCO$_{eq}$), 1.50–1.41 (m, 1H; CHHCHS), 1.45 ppm (s, 3H; CH$_3$CO); ^{13}C NMR (101 MHz, CDCl$_3$, 25°C): $\delta = 145.7$ (s), 111.5 (t), 74.9 (s), 61.2 (t), 44.8 (d), 39.2 (d), 35.3 (t), 31.1 (t), 30.2 (t), 25.5 (t), 22.7 (q), 14.7 ppm (q); MS (CI): m/z (%): 213 (79) [M+1], 135 (100) [M−SCH$_2$CH$_2$OH], 130 (84); HRMS (CI): calcd for C$_{12}$H$_{21}$OS: 213.1313; found: 213.1303.

11: Triethylsilane (5.28 mL, 33.1 mmol) and trimethylsilyltrifluoromethane sulfonate (5.98 mL, 33.1 mmol) were added dropwise sequentially with stirring to a solution of **10** (2.00 g, 6.61 mmol) in CH$_2$Cl$_2$ (100 mL) at 0°C. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate (50 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate (2×25 mL), followed by HCl (1 N, 3×25 mL) and brine (3×25 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to chromatography (EtOAc (2%) in petrol) to give **11** as a colorless oil (700 mg, 50%). $R_f = 0.63$ (EtOAc (20%) in petrol); $[\alpha]_D^{24} = -72.10$ ($c = 0.20$ in CHCl$_3$); IR (neat): $\tilde{\nu} = 1664$ (C=C), 1075 cm^{-1} (C−O); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): $\delta = 5.35–5.28$ (m, 1H; CH=), 4.00 (td, $^2J_{H,H} = 12.0$ Hz, $^3J_{H,H} = 12.0, 2.0$ Hz, 1H; OCHH$_{ax}$), 3.88 (ddd, $^2J_{H,H} = 12.0$ Hz, $^3J_{H,H} = 3.5, 2.0$ Hz, 1H; OCHH_{eq}), 3.14 (dd, $^3J_{H,H} = 12.0, 5.5$ Hz, 1H; CHS), 3.02 (ddd, $^2J_{H,H} = 13.5$ Hz, $^3J_{H,H} = 12.0, 3.5$ Hz, 1H; SCHH$_{ax}$), 2.36 (dt, $^2J_{H,H} = 13.5$ Hz, $^3J_{H,H} = 2.0$ Hz, 1H; SCHH_{eq}), 2.24–2.05 (m, 4H; CH$_2$CO, CHHCHS, CH(CH$_3$)$_2$), 1.80–1.70 (m, 1H; CHHCHS), 1.35 (s, 3H; CH$_3$CO), 0.98 ppm (d, $^3J_{H,H} = 6.5$ Hz, 6H; 2×(CH$_3$)CH); ^{13}C NMR (101 MHz, CDCl$_3$, 25°C): $\delta = 141.7$ (s), 117.2 (d), 73.0 (s), 61.6 (t), 44.5 (d), 39.9 (t), 34.5 (d), 31.3 (t), 29.3 (t), 21.6 (q), 21.2 (q), 15.0 ppm (q); MS (EI): m/z (%): 212 (9) [M]$^+$, 134 (10), 116 (100), 93 (10), 88 (15), 84 (50); elemental analysis: calcd (%) for C$_{12}$H$_{20}$OS (212.4): C 67.9, H 9.50; found: C 68.1, H 9.25.

12:[15] A solution of sodium tetrafluoroborate (3.42 g, 31.2 mmol) in water (1.5 mL) was added to a solution of **2** (944 mg, 4.45 mmol) and benzyl bromide (3.71 mL, 31.2 mmol) in CH$_2$Cl$_2$ (1.5 mL). The resulting mixture was stirred for two days, after which it was extracted with CH$_2$Cl$_2$ (3×15 mL), washed with brine (3×15 mL), dried over magnesium sulfate, filtered, and concentrated under vacuum. The resulting oil was triturated with petrol, and the crystals produced were filtered to give **12** as white prisms (864 mg, 64%). M.p.: 156–159°C (petrol); $[\alpha]_D^{20} = -240.0$ ($c = 0.1$ in CHCl$_3$); IR (neat): $\tilde{\nu} = 3006$ (CH$_2$), 750 cm^{-1} (Ar); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): $\delta = 7.52–7.36$ (m, 5H; ArH), 5.10 (s, 1H; HC=), 4.91 (s, 1H; HC=), 4.80 (d, $^2J_{H,H} = 13.5$ Hz, 1H; CHHPh), 4.65 (d, $^2J_{H,H} = 13.5$ Hz, 1H; CHHPh), 4.17 (ddd, $^2J_{H,H} = 14.5$ Hz, $^3J_{H,H} = 12.0, 2.0$ Hz, 1H; CHHO$_{ax}$), 4.03 (ddd, $^2J_{H,H} = 14.5$ Hz, $^3J_{H,H} = 4.5, 2.0$ Hz, 1H; CHHO$_{eq}$), 3.50 (dt, $^2J_{H,H} = 12.0$ Hz, $^3J_{H,H} = 2.0$ Hz, 1H; CHHS$_{eq}$), 3.38 (dd, $^3J_{H,H} = 13.5, 3.5$ Hz, 1H; CHS), 3.10 (td, $^2J_{H,H} = 12.0$ Hz, $^3J_{H,H} = 12.0, 4.5$ Hz, 1H; CHHS$_{ax}$), 2.51–2.45 (br m, 1H; CHC=C), 2.26–2.25 (br m, 1H; CHH ring), 2.05–1.95 (m, 1H; CHH ring), 1.91–1.60 (m, 4H; CH$_2$ ring), 1.82 (br s, 3H; CH$_3$C=), 1.49 ppm (s, 3H; CH$_3$CO); ^{13}C NMR (101 MHz, CDCl$_3$, 25°C): $\delta = 144.2$ (s), 131.0 (d), 130.4 (d), 129.7 (d), 126.1 (s), 113.0 (t), 75.7 (s), 57.1 (t), 55.9 (d), 44.4 (t), 38.1 (d), 37.5 (t), 35.8 (t), 26.9 (t), 24.6 (t), 22.8 (q), 16.2 ppm (q); MS (ESI): m/z (%): 303 (100) [M]$^+$; elemental analysis: calcd (%) for C$_{19}$H$_{27}$BF$_4$OS (390.3): C 58.5, H 6.97; found: C 58.5, H 6.85.

13:[15] A solution of sodium tetrafluoroborate (2.17 g, 19.8 mmol) in water (1.0 mL) was added to a solution of **11** (600 mg, 2.82 mmol) and benzyl bromide (2.35 mL, 19.8 mmol) in CH$_2$Cl$_2$ (1.0 mL). The resulting mixture was stirred for two days, after which it was extracted with CH$_2$Cl$_2$ (3×10 mL), washed with brine (3×10 mL), dried over magnesium sulfate, filtered, and concentrated under vacuum. The resulting oil was triturated with petrol, and the resulting crystals were isolated by filtration to give **13** as white cubes (428 mg, 50%). M.p.: 165–167°C (petrol); $[\alpha]_D^{20} = -40.0$ ($c = 0.1$ in CHCl$_3$); IR (neat) $\tilde{\nu} = 3005$ (CH$_2$), 1500 (Ar), 749 cm^{-1} (Ar); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): $\delta = 7.60–7.35$ (m, 5H; ArH), 5.32 (br t, $^4J_{H,H} = 2.5$ Hz, 1H; CH=C), 4.87 (s, 2H; CH$_2$Ph), 4.16–4.07 (m, 2H; CH$_2$O), 3.55–3.50 (m, 2H; CHHS$_{eq}$, CHS), 3.29 (ddd, $^2J_{H,H} = 12.0$ Hz, $^3J_{H,H} = 10.0, 6.5$ Hz, 1H; CHHS$_{ax}$), 2.38 (dd, $^2J_{H,H} = 17.0$, $^3J_{H,H} = 5.5$ Hz, 1H; CHHS$_{eq}$), 2.22–2.00 (m, 4H; CH$_2$ ring), 1.37 (s, 3H; CH$_3$CO), 0.94 (d, $^3J_{H,H} = 3.5$ Hz, 3H; CH_3CH), 0.93 ppm (d, $^3J_{H,H} = 3.5$ Hz, 3H; CH_3CH); ^{13}C NMR (101 MHz, CDCl$_3$, 25°C): $\delta = 139.4$ (s), 131.0 (d), 130.4 (d), 129.8 (d), 126.5 (s), 117.0 (d), 73.5 (s), 57.2 (t), 54.6 (d), 45.1 (t), 39.7 (t), 36.6 (t), 34.2 (d), 27.8 (t), 21.2 (q), 20.8 (q), 17.0 ppm (q); MS (ESI): m/z (%): 303 (100) [M]$^+$; elemental analysis: calcd (%) for C$_{19}$H$_{27}$BF$_4$OS (390.3): C 58.5, H 6.97; found: C 58.3, H 7.15.

16: Potassium thioacetate (11.7 g, 105 mmol) was added portionwise (5 portions) to a solution of **15** (16.5 g, 100 mmol) in DMF (160 mL), and more DMF (60 mL) was used to rinse the final portion of thioacetate into the flask. The initially exothermic reaction (40–50°C) was stirred overnight at room temperature. The reaction mixture was diluted with diethyl ether and washed with water (6×50 mL). The aqueous layer was then extracted with diethyl ether (2×50 mL). The combined organic layers were then washed once with brine (50 mL), dried over magnesium sulfate, filtered, concentrated, and the crude residue was distilled under vacuum (44°C, ≈0.9 mbar) to yield **16** as a slightly yellow pungent oil (12.4 g, 77%). $R_f = 0.44$ (EtOAc/petrol = 8:2); IR (neat): $\tilde{\nu} = 1712$ (C=O), 1685 (SC=O); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): $\delta = 2.28$ (s, 3H; CH$_3$), 2.27 (s, 3H; CH$_3$), 1.49 ppm (s, 6H; (CH$_3$)$_2$); ^{13}C NMR (101 MHz, CDCl$_3$, 25°C): $\delta = 206.9$ (s), 195.1 (s), 56.6 (s), 24.6 (q), 24.6 (q), 24.4 ppm (q); MS (CI): m/z (%): 161 (46) [M+1], 119 (69) [M+1−COCH$_3$], 101 (100) [C$_5$H$_9$O$_2$], 85 (51) [C$_5$H$_9$O], 74 (33) [SCOCH$_3$]; HRMS: calcd for C$_7$H$_{13}$O$_2$S: 161.0636; found: 161.0631.

4 (racemate): A solution of sodium thiomethoxide (0.5 mL of a 1 M solution in methanol) was added to a stirred solution of **16** (80 mg, 0.5 mmol) in methanol (5 mL) at room temperature. The reaction was stirred for 180 min before propylene epoxide was added dropwise with a syringe over 5 min. After 4 h the reaction mixture was quenched with saturated ammonium chloride (10 mL) solution and diluted with EtOAc (50 mL). After phase separation the organic layer was washed with water (3×

50 mL), dried over magnesium sulfate, filtered, and concentrated. The residue was dissolved in dichloromethane (0.5 mL), boron trifluoride diethyletherate (50 μL, 0.4 mmol) was added followed by triethylsilane (0.06 mL, 0.4 mmol), and the reaction was allowed to stir overnight. After neutralization with saturated sodium bicarbonate (until pH 7–8), the organic layer was separated, washed with water (3×50 mL), dried over magnesium sulfate, and the solvent was removed under reduced pressure. The oil was purified by column chromatography (EtOAc/petrol=9:1–8:2) to yield **4** as a colorless, pungent liquid (50.5 mg, 79%). R_f=0.40 (EtOAc/petrol=8:2); IR (neat): $\tilde{v}$=2967 (C–H), 1081 cm^{-1} (C–O); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): δ=3.65 (dqd, $^3J_{H,H}$= 11.0, 6.0, 2.0 Hz, 1H; C*H*CH$_2$S), 3.64 (q, $^3J_{H,H}$=6.5 Hz, 1H; CH$_3$C*H*O), 2.69 (dd, $^2J_{H,H}$=13.5 Hz, $^3J_{H,H}$=11.0 Hz, 1H; C*H*HS$_{ax}$), 2.21 (dd, $^2J_{H,H}$= 13.5 Hz, $^3J_{H,H}$=2.0 Hz, 1H; CH*H*S$_{eq}$), 1.31 (s, 3H; C*H$_3$*CHO), 1.17 (d, $^3J_{H,H}$=6.0 Hz, 3H; C*H$_3$*CHCH$_2$S), 1.04 (s, 3H; C*H$_3$*), 1.02 ppm (d, $^3J_{H,H}$= 6.5 Hz, 3H; C*H$_3$*CHO); ^{13}C NMR (101 MHz, CDCl$_3$, 25°C): δ=82.9 (d), 75.2 (d), 40.2 (s), 32.3 (t), 26.3 (q), 22.1 (q), 20.7 (q), 16.7 ppm (q); MS (EI): m/z (%): 161 (100) [M+1], 143 (39) [M−OH], 103 (46) [C$_5$H$_{10}$SH]; HRMS: calcd for C$_8$H$_{17}$OS: 161.1000; found: 161.0992.

18 and **19**: Silver tetrafluoroborate (238 mg, 1.22 mmol) was added to a solution of **4** (90 mg 0.56 mmol) and benzyl bromide (134 μL, 1.12 mmol) in acetone (0.3 mL) in a flask (5 mL) covered with aluminum foil. The reaction mixture was stirred overnight at 40°C, then cooled to 0°C, upon which crystallization occurred. The crude product was purified by column chromatography (methanol (10%) in dichloromethane) to yield **18** and **19** (2:1) as colorless crystals (125 mg, 66%). R_f=0.04 (dichloromethane/MeOH=9:1); m.p.: 146–149°C; IR (neat): $\tilde{v}$=2988 (C–H), 773 cm^{-1} (Ar); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): δ=7.36–7.55 (m, 5H, Ar), 4.91 (d, $^2J_{H,H}$=14.0 Hz, 0.33H; SC*H*HPh), 4.90 (d, $^2J_{H,H}$=14.0 Hz, 0.33H; SCH*H*Ph), 4.71 (d, $^2J_{H,H}$=13.0 Hz, 0.66H; SC*H*HPh), 4.67 (d, $^2J_{H,H}$=13.0 Hz, 0.66H; SCH*H*Ph), 4.47 (q, $^3J_{H,H}$=6.5 Hz, 0.33H; C*H*-(CH$_3$)), 4.28 (dqd, $^3J_{H,H}$=11.0, 6.0, 1.5 Hz, 0.33H; SCH$_2$C*H*O), 3.90 (dqd, $^3J_{H,H}$=12.0, 6.0, 1.5 Hz, 0.66H; SCH$_2$C*H*O), 3.71 (q, $^3J_{H,H}$=6.5 Hz, 0.66H; C*H*(CH$_3$), 3.32 (t, $^2J_{H,H}$=12.0 Hz, $^3J_{H,H}$=12.0 Hz, 0.66H; C*H*HS$_{ax}$) 3.23 (dd, J=12.0, 1.5 Hz, 0.66H; CH*H*S$_{eq}$), 3.01 (dd, $^2J_{H,H}$= 15.0 Hz, $^3J_{H,H}$=11.0 Hz, 0.33H; C*H*HS$_{ax}$), 2.87 (dd, $^2J_{H,H}$=15.0 Hz, $^3J_{H,H}$= 1.5 Hz, 0.33H; CH*H*S$_{eq}$), 1.65 (s, 2H; CH$_3$), 1.61 (s, 1H; CH$_3$), 1.49 (s, 1H; CH$_3$), 1.25–1.19 ppm (m, 8H; CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$, 25°C): δ=130.6 (2×d), 130.1 (d), 130.0 (d), 129.9 (d), 129.8 (d), 127.7 (s), 127.2 (s), 79.8 (d), 74.7 (d), 72.0 (d), 66.9 (d), 57.0 (s), 54.6 (s), 42.6 (t), 38.3 (t), 38.2 (t), 34.4 (t), 22.5 (q), 22.3 (q), 21.2 (q), 21.1 (q), 19.6 (q), 15.9 (q), 15.4 (q), 13.8 ppm (q); MS (ESI): m/z (%): 589 (33) [$2M$+ BF$_4^-$], 251 (100) [M]$^+$; HRMS: calcd for C$_{15}$H$_{23}$OS: 251.1460 [M]$^+$; found: 251.1464.

5: Potassium hydroxide (144 mg, 2.54 mmol) in water (2.2 mL) was added to a stirred solution of **16** (312 mg, 1.95 mmol) in methanol (17 mL). After 10 min at room temperature, (*S*)-propylene oxide (150 μL, 2.14 mmol) was added. The reaction mixture was diluted with diethyl ether after 3 h and quenched with KHSO$_4$ solution (1 N, until pH 4). The organic layer was washed with water (2×50 mL), dried over magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved at −40°C in dry dichloromethane (40 mL), and allyltrimethyl silane (2.10 mL, 13.6 mmol) was added in one portion. Over a period of 5 min, boron trifluoride etherate (1.09 mL, 7.77 mmol) was added dropwise. The reaction mixture was allowed to warm overnight and was quenched at 0°C with saturated sodium bicarbonate (until pH 7–8). The organic layer was separated, washed with water (3× 50 mL), dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The oil obtained was purified by column chromatography (EtOAc/petroleum ether=9:1–8:2) to yield **5** as a pungent liquid (307 mg. 78%). R_f=0.79 (EtOAc/petrol=7:3); [α]$_D^{20}$=−41.9 (*c*=1.0 in CHCl$_3$); IR (neat): $\tilde{v}$=3075 (C=CH$_2$), 1043 cm^{-1} (C–O); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): δ=5.72 (m, 1H; CH$_2$C*H*= CH$_2$), 5.08 (m, 1H; CH$_2$CH=C*H*H), 5.05 (m, 1H; CH$_2$CHCH*H*), 3.84 (m, 1H; SCH$_2$C*H*CH$_3$), 3.56 (ddd, $^2J_{H,H}$=15.0 Hz, $^3J_{H,H}$=6.0, 1.0 Hz, 1H; CH*H*S$_{eq}$), 2.68 (dd, $^2J_{H,H}$=14.0 Hz, $^3J_{H,H}$=11.0 Hz, 1H, C*H*HCH=CH$_2$), 2.16 (1H, dd, $^2J_{H,H}$=14.0 Hz, $^3J_{H,H}$=2.5 Hz, CH*H*HCH=CH$_2$), 2.02 (dd, $^2J_{H,H}$=15.0 Hz, $^3J_{H,H}$=8.0 Hz, 1H; CH*H*S$_{ax}$), 1.51 (s, 3H; C(CH$_3$)$_2$S), 1.07 (d, $^3J_{H,H}$=6.5, 3H; CHC*H$_3$*), 1.04 (s, 3H; C(CH$_3$)$_2$S), 1.01 ppm (d, $^5J_{H,H}$=

1.0, 3H; C*H$_3$*C(CH$_3$)$_2$S); ^{13}C NMR (101 MHz, CDCl$_3$, 25°C): δ=134.2 (d), 117.5 (t), 78.6 (s), 66.4 (d), 43.9 (s), 36.5 (t), 31.7 (t), 25.1 (q), 25.0 (q), 22.1 (q), 21.2 ppm (q); MS (CI): m/z (%): 217 (100) [M+ +NH$_3$], 201 (19) [M+1]; HRMS: calcd for C$_{11}$H$_{21}$OS: 201.1313; found: 201.1312.

20: Benzyl alcohol (186 μL, 1.80 mmol) was added to **5** (72 mg, 0.36 mmol) in dioxane (200 μL). Tetrafluoroboric acid in diethyl ether (54%, 206 μL, 1.65 mmol) was added dropwise to this colorless solution, which immediately turned black. After 24 h the precipitate was washed with petrol (3×50 mL). The product was recrystallized from petrol/ EtOAc to yield **20** (108 mg, 81%). M.p.: decomp. at 152–153°C (petrol/ EtOAc); R_f=0.06 (CH$_2$Cl$_2$/MeOH=9:1); [α]$_D^{20}$=−95.0 (*c*=1.1 in CHCl$_3$); IR (neat): $\tilde{v}$=3006 (CH$_2$), 750 cm^{-1} (Ar); ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): δ=7.55–7.34 (m, 5H; ArH), 5.65 (m, 1H; CH$_2$C*H*= CH$_2$), 5.28–5.20 (m, 2H; CH$_2$CH=C*H*$_2$), 4.73 (d, $^2J_{H,H}$=5.5 Hz, 1H; C*H*HPh), 4.63 (d, $^2J_{H,H}$=5.5 Hz, 1H; CH*H*Ph), 4.08 (m, 1H; SCH$_2$C*H*CH$_3$), 3.29 (dd, $^2J_{H,H}$=12.0 Hz, $^3J_{H,H}$=11.0 Hz, 1H; C*H*HS$_{ax}$), 3.19 (dd, $^2J_{H,H}$=12.0 Hz, $^3J_{H,H}$=2.0 Hz, 1H; CH*H*S$_{eq}$), 3.05 (ddd, $^2J_{H,H}$= 15.5 Hz, $^3J_{H,H}$=4.5 Hz, $^4J_{H,H}$=1.0 Hz, 1H; C*H*$_2$CH=CH$_2$), 2.34 (dd, $^2J_{H,H}$=15.5 Hz, $^3J_{H,H}$=7.5 Hz, 1H; CH$_2$CH=CH$_2$), 1.79 (s, 3H; C(CH$_3$)$_2$S), 1.40 (s, 3H; C(CH$_3$)$_2$S), 1.32 (d, $^3J_{H,H}$=6.5 Hz, 3H; CHCH$_3$), 1.25 ppm (d, $^5J_{H,H}$=1.0, 3H; C*H$_3$*C(CH$_3$)$_2$S); ^{13}C NMR (100 MHz, CDCl$_3$/ [D$_4$]MEOD, 25°C): δ=130.4 (d), 130.2 (d), 129.9 (d), 129.8 (d), 126.5 (s), 120.2 (t), 80.2 (s), 63.8 (d), 60.1 (s), 42.3 (t), 37.4 (t), 35.8 (t), 21.4 (q), 21.1 (q), 16.7 ppm (2×q); MS (CI): m/z (%): 291 (31) [M]$^+$, 275 (23) [M−CH$_3$], 201 (25) [M−CH$_2$Ph+1], 91 (100) [CH$_2$Ph]$^+$; HRMS: calcd for C$_{18}$H$_{27}$OS: 291.1777 [M]$^+$; found: 291.1779.

Representative procedure for Method A:[7] Powdered potassium hydroxide (85%, 40 mg, 0.60 mmol) was added with stirring to a mixture of benzaldehyde (30 μL, 0.30 mmol) and **12** (117 mg, 0.30 mmol) in ethanol (anhydrous, 0.9 mL) at −50°C. The reaction mixture was stirred at −50°C for 48 h. The mixture was concentrated under vacuum, and the residue was dissolved in CH$_2$Cl$_2$ (25 mL). The reaction mixture was filtered, the filtrate was dried over magnesium sulfate, filtered, and the filtrate concentrated under vacuum. The residue was subjected to chromatography (EtOAc (2%) in petrol) to afford the product as a white solid (32 mg, 54%, *trans/cis*=72:28, 89% *ee*).

Representative procedure for Method B:[7] EtP$_2$ base (43 μL, 0.13 mmol) was added with stirring to a mixture of benzaldehyde (13 μL, 0.13 mmol) and **12** (50 mg, 0.13 mmol) in CH$_2$Cl$_2$ (0.9 mL) at −78°C. The reaction mixture was stirred at −78°C for 1 h, after which brine (1 mL) was added. The reaction mixture was extracted with CH$_2$Cl$_2$ (3×5 mL), and the organic phases were combined, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to chromatography (EtOAc (2%) in petrol) to afford the product as a white solid (19 mg, 75%, *trans/cis*=99:1, 87% *ee*).

Acknowledgements

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